SUPPORT FOR THE AMENDMENTS

The amendment to Claim 1 and newly-added Claims 28 and 29 are supported by the specification, in particular by page 4, line 29 to page 5, line 5, and page 5, lines 28-32. Accordingly, no new matter is believed to have been added to the present application by the amendments submitted above.

REMARKS

Claims 1-15, 17-21, 24, 25 and 27-29 are now pending. Favorable reconsideration is respectfully requested.

Applicants would like to thank Examiner Vivlemore for the helpful and courteous discussion held with their representative on October 29, 2009. During that meeting, the amendment to Claim 1 presented above was discussed. The differences between the claimed oligonulceotides and the cited references were also discussed. The following remarks expand on the discussion with the Examiner.

The present invention relates to a double-stranded oligonucleotide comprising two strands of 19 to 23 nucleotides, each strand consisting, from 5' to 3', of a sequence of 17 to 21 ribonucleotides and two deoxyribo- or ribonucleotides, the 17 to 21 ribonucleotide RNA sequences of said strands being complementary and the two nucleotides of the 3' ends being protruding, where the RNA sequence of the sense strand or positive strand is that of a fragment of a transcript of an α, α' or β subunit of a CK2 protein kinase, selected from the group consisting of:

a) a fragment of a transcript of an α subunit included between positions 18-74, 259-279, 565-585, 644-664, 720-750, 808-831 and 863-885, from the ATG codon, with reference to the sequence SEQ ID NO: 88,

b) a fragment of a transcript of an α' subunit included between positions 49-69, 132-152, 306-326, 367-387, 427-447, 451-471, 595-615, 735-755, 827-847, 868-888, 949-969 and 988-1008, from the ATG codon, with reference to the sequence SEQ ID NO: 89,

c) a fragment of a transcript of a β subunit included between positions 80-100, 116-137, 164-208, 369-389, 400-420, 527-591 and 613-643, from the ATG codon, with reference to the sequence SEQ ID NO: 90, and

d) a fragment of 17 to 21 bases exhibiting at least 80% identity with the fragments defined in a), b), and c),

where the double-stranded oligonucleotide inhibits specifically more than 80% of the expression of the CK2 alpha, alpha' or beta subunit and of the corresponding mRNA in human cell culture at a concentration of between 1 and 200 nM.

See Claim 1.

The rejection of the claims under 35 U.S.C. §103(a) over Wyatt in view of Bass and Fosnaugh et al. is respectfully traversed. The cited references fail to suggest the claimed oligonucleotide.

Wyatt discloses antisense modulation of casein kinase 2-beta expression. See the Abstract. This reference fails to disclose siRNA.

Bass provides a very brief overview of RNA interference (RNAi). This reference is silent with respect to targeting an α, α' or β subunit of a CK2 protein kinase as specified in Claim 1. This reference notes that the use of RNAi in mammalian cells "has been problematic" (see page 428, first column, first paragraph.

Fosnaugh et al. relates to RNA interference mediated inhibition of adenosine A1 receptor (ADORA1) gene expression using short interfering RNA. See the Abstract. This reference is silent with respect to targeting an α, α' or β subunit of a CK2 protein kinase as specified in Claim 1.

The claims of the present application recite specific target sequences of the α, α' or β subunit of a CK2 protein kinase as set forth in Claim 1. The rationale for the rejection is that Wyatt discloses antisense modulation of the relevant gene, so it would be obvious to target the gene with siRNA.

However, Wyatt teaches (Table 1) a list of 85 antisense oligodeoxynucleotides (ASO) targeted to the different regions that cover the entire length of the human CK2-beta RNA (5'UTR, coding regions, the introns, the intron-exon junctions, 3'UTR). These ASO inhibit human CK2-beta mRNA expression with various efficiencies ranging from 0 % to 91 % (Table 1).

Contrary, to what is stated by the Examiner page 7 of the pending Office Action, the target of an ASO is an expression which is known and perfectly understood by one of ordinary skill in the art. The target or the target site corresponds to the particular sequence of the RNA to which the ASO binds to or to which the ASO is complementary (see Wyatt, example 15, column 46, lines 14 to 17 and column 47, lines 56-57. In the Table 1 of Wyatt, the target site (20 nucleotides) is indicated by the first (5' most) nucleotide position in the mRNA sequence.

SEQ ID NO: 3 of Wyatt et al. corresponds to SEQ ID NO: 90 in the present application. Taking SEQ ID NO: 3 as human CK2-beta mRNA reference sequence, Wyatt teaches ASOs SEQ ID NO: 38 to 95. Among, these ASOs, 13 inhibit more than 80 % of human CK2-beta mRNA expression. These most efficient ASOs target positions 267-286, 348-367, 363-382, 373-392, 380-399, 409-428, 578-597, 674-693, 822-841, 832-851, 860-879 and 1035-1054 of human CK2-beta mRNA.

However, one of ordinary skill in the art could not arrive at the claimed invention because the cited references neither disclose nor suggest the human CK2 beta subunit mRNA sites (i.e. positions 420-440, 456-477, 504-548, 709-729, 740-760, 867-931 and 953-983) which are targeted by the claimed siRNAs.

Positions 420-440, 456-477, 504-548, 709-729, 740-760, 867-931 and 953-983 of human CK2 beta subunit mRNA correspond to positions 80-100, 116-137, 164-208, 369-389, 400-420, 527-591 and 613-643 from the ATG start codon (the ATG codon is at positions 341 to 343; see SEQ ID NO: 90 in the sequence listing of the present application).

The Examiner considers that at the time of filing those of ordinary skill in the art would make the antisense SEQ ID NO: 60 of Wyatt which target positions 423 to 444 of human CK2 beta subunit mRNA into an siRNA according to the teaching of Fosnaugh et al.. He or she would thus arrive at the claimed siRNA which target positions 420 to 439 of human CK2 beta subunit mRNA (SEQ ID NO: 60 is targeted to a region sharing 16 nucleotides with the elected target region represented by SEQ ID NO: 26) by design choice and routine optimization to find siRNAs having the best properties or desired application.

However, it is only with the foreknowledge of the invention that among hundreds of antisense targeting human CK2 beta which are disclosed in Wyatt, the Examiner has been capable of identifying one particular antisense targeting human CK2 beta which is not the most efficient antisense in human cells.

On page 7 of the pending Office Action, the Examiner points out that she doest not understand how an antisense targeted to human CK2 and a siRNA targeted to this same gene would not have the same target.

Again, it is only with the foreknowledge of the claimed siRNAs and by making a fundamentally incorrect assertion that the Examiner is linking a particular antisense targeted to human CK2 beta to the claimed siRNA targeting the same mRNA.

To find some motivation to make an antisense into a siRNA the skilled artisan needed to find some teaching or suggestion in the prior art or the common general knowledge that antisense targeted to human CK2 and a siRNA targeted to the same gene would have the same target.

However, Bass teaches that antisense and siRNA are two different techniques which are used to prevent expression of particular genes as mentioned in Bass: "Further siRNA techniques in mammalian cells have some of the same drawbacks associated with antisense RNA, another technique used to prevent expression of particular genes." (page 428, last column, last paragraph to page 429, first column, beginning of first paragraph).

Therefore, since siRNA and antisense are considered as two different techniques, one of ordinary skill in the art would not make an antisense into an siRNA to obtain a functional siRNA.

Furthermore, as explained in the response to the first Office Action, siRNAs and antisense oligonucleotides were known to be totally different type of molecules that use different mechanisms of action to inhibit gene expression (see for example, the introduction of Bertrand et al., BBRC, 2002, 296, 1000-1004; Annex 1).

ASOs consist of single-strand of 12-22 oligodeoxynucleotides which are complementary to the target mRNA sequence. Binding of the ASO to target mRNA results in steric inhibition of translation by ribosomal complex but more importantly stimulates degradation of the mRNA via RNase H.

siRNA consist of short RNA duplexes of 21-23 ribonucleotides which are incorporated into a ribonucleoprotein-endonuclease complex termed "RNA Induced Silencing Complex" (RISC). The siRNAs are then unwound and the antisense strand directs the complex to target the specific endogenous RNA sequence. The target RNA transcript is then bound and degraded by the endonuclease activity of RISC.

Nothing in the common general knowledge at the time of filing of the present Application indicates that because siRNA and ASO bind to a portion of a RNA to silence gene expression they would bind to the same region of this RNA.

In addition, gene silencing by siRNA and ASO does not result solely on the binding of the siRNA or ASO to its target. It results from the interaction of siRNA and ASO with different cellular partners (RISC versus RNaseH).

Therefore, there are fundamental differences in the sequence features which correlate with silencing efficacies for ASO and siRNA (see for example Z.J. Lu and D.H. Mathews, Nucleic Acids Research, 2008, 36, n°11; Annex 4 in the response to the first Office Action).

Consequently, different mRNA targets are used by antisense and siRNA to achieve efficient gene silencing in mammalian cells.

For example, Bertrand et al., which compare antisense and siRNA targeting the same gene uses antisense and siRNA targeted to totally different regions of the GFP RNA: the antisense is targeted to position 1198 and the siRNA to position 1522 (see material and methods, middle of last paragraph page 1000 of Bertrand et al.). A copy of Bertrand et al. is submitted herewith.

This is also confirmed by the comparison of the antisense of Wyatt et al. with the claimed siRNAs. The claimed siRNAs which inhibit more than 80% of human CK2 beta mRNA expression target positions 420-440, 456-477, 504-548, 709-729, 740-760, 867-931 and 953-983. The antisense of Wyatt et al. which inhibit more than 80% of human CK2 beta mRNA expression target different positions (i.e., 267-286, 348-367, 363-382, 373-392, 380-399, 409-428, 578-597, 674-693, 822-841, 832-851, 860-879 and 1035-1054).

Therefore, it is fortuitous that one of the antisense oligonucleotides disclosed in Wyatt binds to a sequence of the CK2 beta subunit transcript that has partial overlap with the sequence of the CK2 beta subunit transcript that is bound by one of the claimed siRNA.

It is only with the foreknowledge of the invention that the Examiner has found the antisense SEQ ID NO: 60 which is disclosed by Wyatt.

In addition, the skilled artisan would not make the antisense SEQ ID NO: 60 of Wyatt into an siRNA for the reasons explained above.

Therefore, the claimed siRNAs are not obvious in light of the antisense oligonucleotides in Table 1 of Wyatt.

Furthermore, the identification of siRNAs with high efficiency and high specificity to its human CK2 subunit target would not have been considered routine work for one of ordinary skill in the art at the time the invention was made for the reasons already explained in the response to the second Office Action.

In addition, In addition, in the response to the second Office Action, the Inventors have provided additional data demonstrating that:

(1) the claimed siRNA produce an effect (phenotype) in the CK2 knock-down cells that is due to the silencing of the corresponding CK2 subunit and not to the silencing of a non-specific target (no off-target gene silencing effect; Annexes I and II to IV and item 2.3 of the response to the second Office Action,

(2) the claimed siRNA have an exquisite specificity compared to other known CK2 kinase inhibitors (Annexes I to III and item 2.3 of the response to the second Office Action),

(3) the claimed siRNA have an antitumoral activity in vivo (Annex V and item 2.3 of the response to the second Office Action).

These striking effects would not have been expected from the cited references, since the references taken in combination fail to suggest the specific target sequences recited in Claim 1.

In view of the foregoing, the claimed double stranded oligonucleotide is not obvious over the combination of Wyatt in view of Bass and Fosnaugh et al. Accordingly, the subject matter of the pending claims is not obvious over those references. Withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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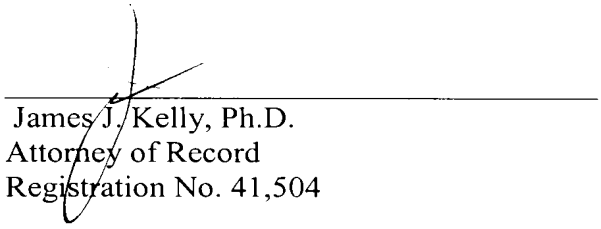

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